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From a Theoretical Framework of Human Exposure and Dose Assessment to Computational System Implementation: The Modeling ENvironment for TOtal Risk Studies (MENTOR)

Panos G. Georgopoulos [a] & Paul J. Lioy [a]
[a] Exposure Measurement and Assessment Science Division , Environmental and Occupational Health Sciences Institute (EOHSI), a Joint Institute of UMDNJ- Robert Wood Johnson Medical School and Rutgers University , Piscataway, New Jersey, USA
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FROM A THEORETICAL FRAMEWORK OF HUMAN EXPOSURE AND DOSE ASSESSMENT TO COMPUTATIONAL SYSTEM IMPLEMENTATION: THE MODELING ENVIRONMENT FOR TOTAL RISK STUDIES (MENTOR)

Panos G. Georgopoulos, Paul J. Lioy

Exposure Measurement and Assessment Science Division, Environmental and Occupational Health Sciences Institute (EOHSI), a Joint Institute of UMDNJ- Robert Wood Johnson Medical School and Rutgers University, Piscataway, New Jersey, USA

Georgopoulos and Lioy (1994) presented a theoretical framework for exposure analysis, incorporating multiple levels of empirical and mechanistic information while characterizing/reducing uncertainties. The present review summarizes efforts towards implementing that framework, through the development of a mechanistic source-to-dose Modeling ENvironment for TOtal Risks studies (MENTOR), a computational toolbox that provides various modeling and data analysis tools to facilitate assessment of cumulative and aggregate (multipathway) exposures to contaminant mixtures.

MENTOR adopts a "Person Oriented Modeling" (POM) approach that can be applied to either specific individuals or to populations/subpopulations of interest; the latter is accomplished by defining samples of "virtual" individuals that statistically reproduce the physiological, demographic, etc., attributes of the populations studied. MENTOR implementations currently incorporate and expand USEPA's SHEDS (Stochastic Human Exposure and Dose Simulation) approach and consider multiple exposure routes (inhalation, food, drinking water intake; non-dietary ingestion; dermal absorption). Typically, simulations involve: (1) characterizing background levels of contaminants by combining model predictions and measurement studies; (2) characterizing multimedia levels and temporal profiles of contaminants in various residential and occupational microenvironments; (3) selecting sample populations that statistically reproduce essential demographics (age, gender, race, occupation, education) of relevant population units (e.g., census tracts); (4) developing activity event sequences for each member of the sample by matching attributes to entries of USEPA's Consolidated Human Activity Database (CHAD); (5) calculating intake rates for the sample population members, reflecting physiological attributes and activities pursued; (6) combining intake rates from multiple routes to assess exposures; (7) estimating target tissue doses with physiologically based dosimetry/toxicokinetic modeling.

The theoretical and conceptual framework of Georgopoulos and Lioy (1994) outlined the needs and challenges facing the use of probabilistic source-to-dose analyses of exposure as an integral part of environmental health risk assessments. The ideas and framework of the 1994 article led to work towards the development of a modular, comprehensive, source-to-dose modeling system; this work has been funded by a number of organizations, including ATSDR and USDOE (these and other acronyms that appear throughout the article are expanded in Tables 1 and 2). In 1998, this development was accelerated through the establishment of a "University Partnership Agreement (UPA)" between USEPA's National Exposure Research Laboratory (NERL) and the Environmental and Occupational Health Sciences Institute (EOHSI), and these efforts resulted in the evolution of the Modeling ENvironment for TOtal Risk studies (MENTOR). The conceptual framework underlying the development of MENTOR is depicted schematically in Figure 1. This diagram represents an

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Address correspondence to Panos G. Georgopoulos, Exposure Management and Assessment Science Division, Environmental and Occupational Health Sciences Institute (EOHSI), 170 Frelinghuysen Road, Room 308, Piscataway, NJ 08854. E-mail: panosg@ccl.rutgers.edu

TABLE 1. List of acronyms that appear in this article

3MRA	Multimedia, Multipathway, Multirecptor Risk Assessment, Version 3
ADIFOR/ADIC	Automatic Differention for FORTRAN Code/Automatic Differention for C
AERMOD	AMS/EPA Regulatory Model Improvement Committee Model
ANN	Artificial Neural Network
ARAMS	Adaptive Risk Assessment Modeling System
ATSDR	Agency for Toxic Substances and Disease Registry
BMCMC	Bayesian Markov Chain Monte Carlo
BME	Bayesian Maximum Entropy
CALMET	CALifornia METeorological model/photochemical model
CALPUFF	CALifornia PUFF model
CAMx	Comprehensive Air quality Model with extensions
CART	Classification and Regression Tree
CATS	Contaminants in Aquatic and Terrestrial ecoSystems
CMAQ	Community Multiscale Air Quality model
EOHSI	Environmental and Occupational Health Sciences Institute
EPANET	Environmental Protection Agency water NETwork model
ERDEM	Exposure Related Dose-Estimating Model
FACT	Flow And Contaminant Transport
FEOM	Fast Equivalent Operational Model
FLD	Fisher's Linear Discriminant
GMS	Groundwater Modeling System
GRASS	Geographic Resources Analysis Support System
HDMR	High Dimensional Model Representation
HYPACT	Hybrid Particle And Concentration Transport Model
ISC	Industrial Source Complex model
KNN	K-Nearest Neighbor
MCMC	Markov Chain Monte Carlo
MENTOR	Modeling ENvironment for TOtal Risk studies
MM5	Fifth-Generation NCAR/Penn State Mesoscale Model
MODFLOW	MODular three-dimensional finite-difference ground-water FLOW model
PBTK	Physiologically Based Toxicokinetic
PD	Pharmacodynamic
QSAR	Quantitative Structure Activity Relationships
RAMS	Regional Atmospheric Modeling System
RPNN	Robust Polynomial Neural Network
SHEDS	Stochastic Human Exposure and Dose Simulation
SIMCA	Soft Independent Modeling of Chemical Analogy
SMOKE	Sparse Matrix Operator Kernel Emissions
SRSM	Stochastic Response Surface Method
STRF	Spatio-Temporal Random Field
SVM	Support Vector Machines
TCE	Trichloroethylene
USDOE	US Department of Energy
USEPA	US Environmental Protection Agency
VOC	Volatile Organic Compound

expansion of the bi-directional modeling approach initially described in the 1994 article. Ongoing and planned work will interface the currently operational source-to-dose analysis components of MENTOR with a DOse-Response Information ANalysis system (DORIAN), that will incorporate molecular and cellular level data (ebCTC 2005; Welsh and Georgopoulos 2005), as well as with a REmediation Analysis (REA) system, that will facilitate the characterization of the impact of alternative remediation/control strategies on human exposure and risk. The overall goal of MENTOR is to provide state-of-the-art tools that enhance quantitative risk assessments for individuals and populations and to identify critical variables for use in epidemiological investigations.

MENTOR, as a computational environment, has evolved from a prototype Exposure and Dose Modeling and Analysis System (EDMAS) (Georgopoulos et al. 1997; Roy and Georgopoulos 1997; Walia and Georgopoulos 1997) which provided a unified framework for linking biological processes

TABLE 2. Summary information on sample databases currently utilized by applications of MENTOR

Database Type	Database Acronym	Database Full Name	Database Developer	URL and/or Literature Reference
Environmental Releases	HazDat	Hazardous Substance Release and Health Effects Database	ATSDR	http://www.atsdr.cdc.gov/hazdat.html (ATSDR 2001)
	NEI	National Emission Inventory	USEPA	http://www.epa.gov/ttn/chief/net/ (USEPA 2002)
	TRI	Toxics Release Inventory	USEPA	http://www.epa.gov/tri/ (USEPA 1998a)
Environmental Concentrations	AQS	Air Quality System	USEPA	http://www.epa.gov/ttn/airs/airsaqs/
	CEP	Cumulative Exposure Project	USEPA	Rosenbaum et al. 1999; USEPA 2001b
	EMAP	Environmental Monitoring and Assessment Program	USEPA	http://www.epa.gov/emap/ (USEPA 1997; Eilers et al. 1987)
	NATA	National Air Toxics Assessment	USEPA	http://www.epa.gov/ttn/atw/nata/ (Rosenbaum et al. 1999; USEPA 2001b)
	NAWQA	National Water Quality Assessment Data Warehouse	USGS	http://water.usgs.gov/nawqa/ (USGS 1999; USGS 2002; Hamilton 2000)
	NGA	National Geochemical Atlas	USGS	http://tin.er.usgs.gov/metadata/ofr-98–622.faq.html
	NWIS	National Water Information System	USGS	http://waterdata.usgs.gov/nwis (Kinerney 2001)
	ORCA	Ocean Resources Conservation and Assessment	NOAA	(Lauenstein and Cantillo 1998)
	SDWIS/FED	Safe Drinking Water Information System/Federal Version	USEPA	http://www.epa.gov/safewater/sdwisfed/sfed2.html (USEPA 1998b)
	STORET	Storage and Retrieval	USEPA	http://www.epa.gov/storet/
	TDS	Total Diet Study	USFDA	http://www.cfsan.fda.gov/~comm/tds-hist.html (IOM 2001)
	WQN	Water Quality Network	USGS	Alexander et al. 1998
Biomarker Data	NHANES II & III	2nd and 3rd National Health and Nutrition Examination Survey	CDC	http://www.cdc.gov/nchs/nhanes.htm (NCHS 1980)
	NHEXAS	National Human Exposure Assessment Survey	USEPA	http://www.epa.gov/heasd/edrb/nhexas.htm Lebowitz et al. 1999; Ryan et al. 2001; Echols et al. 1999
Other Data Supporting Exposure and Risk Assessments	AHS	American Housing Survey	US Bureau of Census	http://www.census.gov/hhes/www/housing/ahs/ahs.html (USCB 2002)
	CHAD	Consolidated Human Activity Database	USEPA	http://www.epa.gov/chadnet1/ (McCurdy et al. 2000; McCurdy 1994; USEPA 2001a)
	CSFII	Continuing Survey of Food Intakes by Individuals	USDA	http://www.barc.usda.gov/bhnrc/foodsurvey/Products9496.html (Tippett et al. 2000)

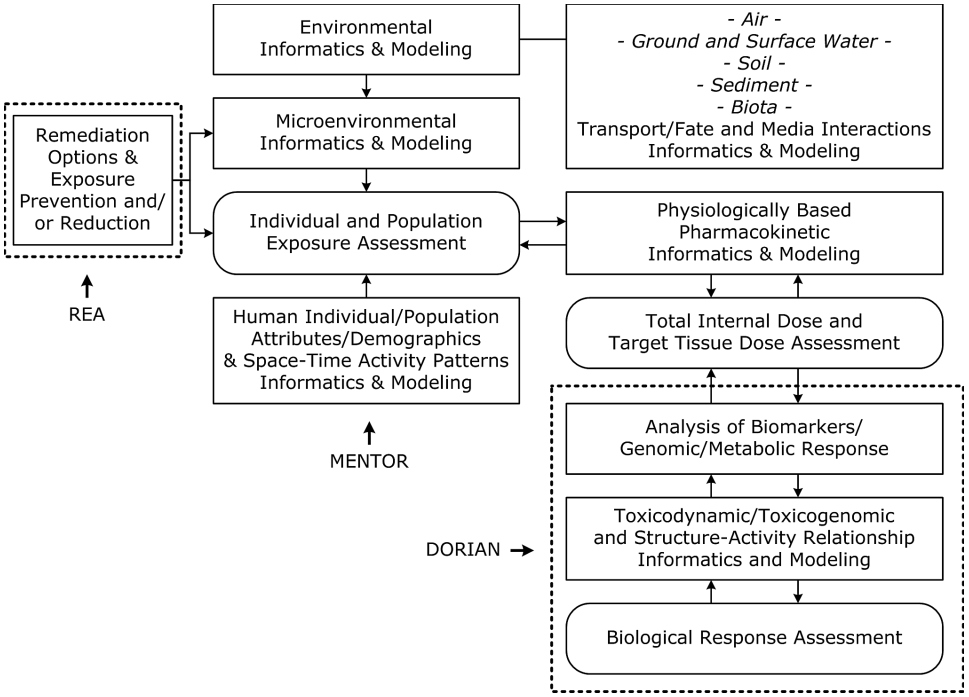

FIGURE 1. The Modeling Environment for Total Risk (MENTOR) approach for integrated analysis and interpretation of human exposure in a source-to-dose framework; components that are currently in development phase are identified in this diagram by a dashed line and correspond to the Remedial Analysis (REA) and Dose-Response Information Analysis (DORIAN) systems.

(toxicokinetics) with environmental and microenvironmental processes and exposure models. The first applications and performance tests of EDMAS included studies of exposures to benzene, ozone, indoor air, chloroform, hazardous wastes, etc. involving inhalation as well as ingestion and dermal contact.

The objective of the MENTOR project has been been to develop, apply and evaluate state-of-the-art modeling methods for a wide range of environmental applications, that utilize existing models, when available, or provide new approaches to "fill gaps" in the source-to-dose sequence. MENTOR links state-of-the art predictive models of environmental fate/transport and of human exposure and dose; these models are coupled with up-to-date national, regional, and local databases of environmental, microenvironmental, biological, physiological, demographic, etc. parameters. Thus MENTOR is not a "new model"; it is an evolving open computational toolbox, containing both "pre-existing" and new tools, intended to facilitate consistent multiscale source-to-dose modeling of exposures to multiple contaminants, for individuals and populations.

Two implementations of MENTOR are currently available; they both incorporate USEPA's Stochastic Human Exposure and Dose Simulation (SHEDS – Burke et al. 2001) approach for treating population activity patterns. MENTOR/SHEDS-1A (MENTOR/SHEDS for "One Atmosphere (1A)" applications) characterizes simultaneous exposures to multiple atmospheric contaminants, taking into account their physical and chemical interactions, for individuals and/or populations (USEPA 2004a; Georgopoulos et al. 2005a, 2005b). MENTOR/SHEDS-4M quantifies aggregate and cumulative exposures and doses of individuals and populations for Multiple co-occurring contaminants and Multimedia, Multipathway, Multiroute exposures "(4M)" (Georgopoulos et al. 2005c; USEPA 2004b).

These implementations of MENTOR incorporate a range of "tools" for modeling environmental and biological processes, for sensitivity and uncertainty analysis, and for formal model reduction.

Initial applications of MENTOR focused on diverse environmental health problems that affect the US, including source-to-dose population exposures to co-occurring PM2.5, ozone and air toxics

for Philadelphia, PA; source-to-dose modeling of multimedia population exposures to co-occurring arsenic and TCE; outdoor (potential) regional ozone exposure modeling for the northeast US for impact on regulatory accountability; exposures of populations to Hg/MeHg through food consumption; children's exposure to organophosphate pesticides; etc. Ongoing MENTOR studies include simulations of the plume and the associated human exposures to contaminants released from the fire and collapse of the World Trade Center on September 11, 2001. Many of these applications are briefly discussed in the present review; for detailed information the reader is referred to documents that are available either in the peer-reviewed literature or publicly accessible via the web at http://ccl.rutgers.edu.

BACKGROUND

In recent years numerous modeling tools were developed by various organizations to support quantitative exposure analyses and assessments. As part of the development effort for the TRIM (Total Risk Integrated Methodology) modeling system (USEPA 1999a), the USEPA conducted an extensive review of models, available at the time, that were considered relevant to exposure assessments. These models typically focus on a particular process or on certain components of the source-to-dose sequence. Furtaw (2001) specifically reviewed exposure modeling activities at USEPA-NERL and summarized developments regarding Models-3/Community Multiscale Air Quality (CMAQ) model, SHEDS, ERDEM and FRAMES-3MRA. A technical report completed for the MENTOR project (Johnson 2002) reviewed in detail the attributes and the evolution of comprehensive inhalation exposure modeling systems that have been developed over the years. Included were NEM/pNEM (National Exposure Model and Probabilistic National Exposure Model), APEX (Air Pollution Exposure) Model – a component of TRIM, and HAPEM (Hazardous Air Pollutant Exposure Model) families of models. Another review, focusing on "person-oriented" modeling and multimedia models for aggregate and cumulative exposures (including Lifeline, CARES, Calendex, etc.) can be found in Price et al. (2003).

MENTOR has been designed to incorporate a wide range of the types of algorithms and databases utilized in the models mentioned above, and in particular in the models under continuing development at USEPA-NERL. The MENTOR toolbox is in fact an open and "flexible" system that provides components for performing either simple (screening) or detailed (comprehensive) simulations at various scales and levels of detail. For example, as mentioned earlier, the SHEDS methodology developed by Özkaynak and coworkers (Burke et al. 2001) was modified, expanded to include biological process modeling, and incorporated into MENTOR. Included in MENTOR are also interactive links with the Consolidated Human Activity Database (CHAD) (McCurdy et al. 2000) for consistent definition of population characteristics and activity events needed to establish intensity and patterns of exposure (Georgopoulos et al. 2005a, 2005c).

Consistent with the concepts presented previously by Georgopoulos and Lioy (1994), MENTOR can be used for both "Individual Based Exposure Modeling" (IBEM) and "Population Based Exposure Modeling" (PBEM) approaches. Both these approaches employ a "Person Oriented Modeling" (POM) formulation, i.e. they are driven by the attributes and activities of the exposed "real" and/or "virtual" individual(s). While IBEM implementations utilize the information relevant to "actual" individuals (and produce exposure and dose estimates specific to each one of them), the PBEM implementations focus on the statistical characterization of the exposures and doses of selected populations (at the census tract, county, or state etc. level). Thus, the questions posed by any particular environmental health problem can be tailored to small sets of individuals potentially at risk or to larger populations or subpopulations of interest.

Methods

The MENTOR Approach The "computational toolbox" of MENTOR (shown schematically in Figure 2) contains modules that facilitate the exposure/risk assessor in performing the following 7 components/steps of a comprehensive probabilistic source-to-dose analysis (summarized schematically in Figure 3):

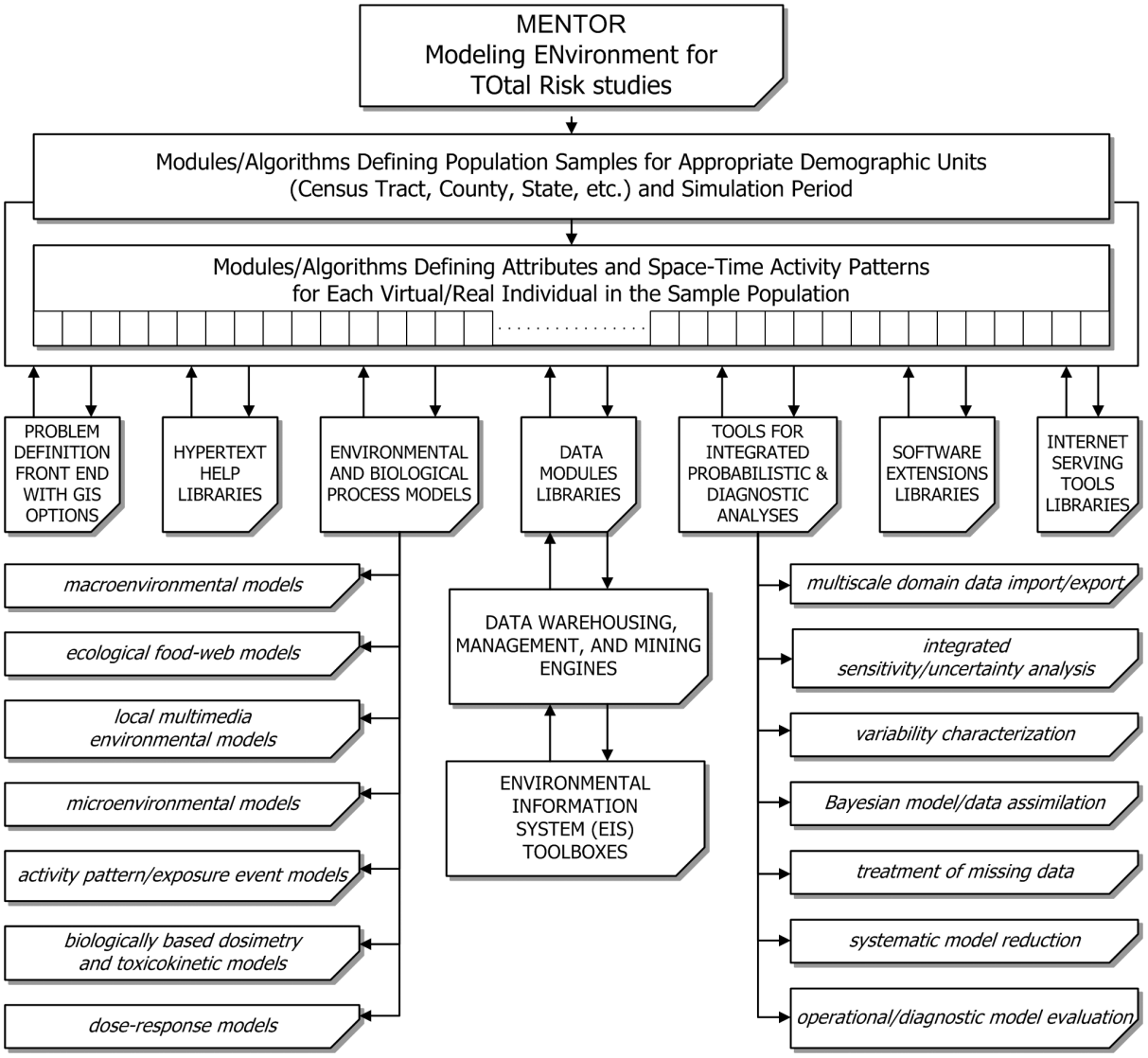

FIGURE 2. Components/modules of the MENTOR computational toolbox.

1. Estimation of the multimedia background levels of environmental contaminants (air, water, soil, food, etc.), for the area/locations where the population of interest resides, through extraction/processing of information from the outcomes of selected comprehensive environmental models (such as USEPA's Models-3/CMAQ for air pollutants; USEPA's EPANET for water-borne contaminants in municipal networks, USGS's MODFLOW or USDOE's FACT for groundwater contaminant transport, etc.) and/or from measurements obtained in field studies. Tools utilized in these analyses include GIS (Geographic Information Systems; specifically GRASS and ESRI's ArcGIS) and RDBMS (Relational Database Management Systems, such as MySQL and Oracle) based components. "Subgrid" (e.g. census tract or neighborhood scale) interpolation/characterization of ambient information is performed through computational tools that utilize spatiotemporal information from models and monitors in a SpatioTemporal Random Field (STRF) or, more generally, a BME (Bayesian Maximum Entropy) framework, as discussed in the following.

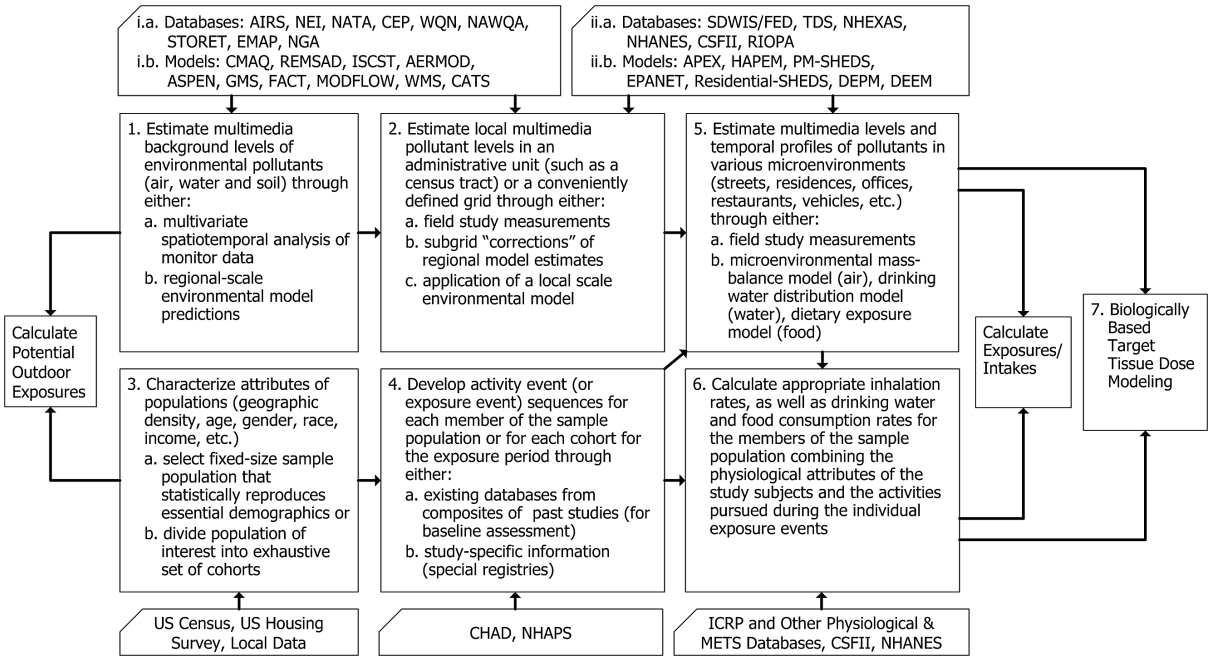

FIGURE 3. The MENTOR framework for assessing cumulative/aggregate exposures and doses for multiple multimedia contaminants.

2. Estimation of multimedia levels (indoor air, drinking water, soil/dust, food, etc. concentrations) and temporal profiles of environmental contaminants in various microenvironments such as residences, offices, restaurants, vehicles, etc. are calculated through microenvironmental steady-state or dynamic mass-balance model simulations, supplemented by information from empirical databases.
3. Characterization of individual attributes (for IBEM applications), or selection of sample populations so as to statistically reproduce essential demographics (age, gender, race, occupation, education) of the population unit used in the assessment (for PBEM).
4. Development of activity event sequences for each "actual" individual from study-specific data (for IBEM applications) or for each "virtual" member of the sample population by matching her/his attributes to entries of USEPA's CHAD for PBEM applications.
5. Calculation of (inhalation, oral, etc.) intake rates for the actual or virtual individuals constituting the sample population considered, based on the physiological attributes of the study subjects and the specific activities pursued during the individual exposure events.
6. Combination of intake rates with the corresponding multimedia microenvironmental concentrations of the contaminant, for each activity event, to assess exposures.
7. Estimation of target tissue doses (e.g., lung deposition and clearance of fine particles; kidney and liver dose and elimination, etc.) through physiologically-based dosimetry and Physiologically Based Toxicokinetic (PBTK) modeling.

The environmental, microenviromental, and biological process modeling tools (modules) available within MENTOR are complemented by various modules for diagnostic model and data analyses. These modules implement a variety of powerful novel techniques including, e.g., Bayesian model/data fusion ("calibration") methods that utilize highly optimized Markov Chain Monte Carlo sampling; systematic mathematical model reduction to Fast Equivalent Operational Models (FEOMs) via HDMR (High Dimensional Model Representation) methods; sensitivity/uncertainty analysis via combined Surface Response Methods (SRSM) and Automatic Differentiation techniques; comparative pattern recognition in field data and model outcomes, etc.

The bidirectional nature of the MENTOR approach can in fact be used either prospectively or retrospectively to establish the exposure/dose of concern; to support the analysis and evaluation of data collected in field or laboratory studies; or to assist in designing new or augmenting current experiments on toxicant characterization for the resolution of current or "old" problems. It can also be used iteratively to characterize new problems that are evolving, or refine hypotheses on current problems, as new or additional information becomes available.

Using the preceding discussion as a guide for understanding the basic philosophy and structure of MENTOR, the following subsections describe the range of modeling tools that have been developed and are currently available. They further present information on selected applications, illustrating the progress made in implementing a probabilistic source-to-dose modeling system since the publication of Georgopoulos and Lioy (1994).

MENTOR Modules – Process and Activity Models

Macroenvironmental models As mentioned in the introduction, MENTOR was designed to operate in conjunction with widely used and tested environmental models for fate/transport in different media, such as Models-3/CMAQ (USEPA 1999b), CAMx (ENVIRON 2004), ISC/AERMOD (USEPA 1998c), CALPUFF (Scire et al. 2000), MM5 (Grell et al. 1995; NCAR 2004), RAMS/HYPACT (Walko et al. 1999; Walko and Tremback 2001), EPANET (Rossman 2000), MODFLOW (Guiguer and Franz 1996), GMS (BYU 2003), FACT (Hamm and Aleman 2000), ARAMS (Dortch and Gerald 2004), etc.

Priority was given in developing linkages and data transfer modules for environmental fate/transport models included in USEPA's list of the Council for Regulatory Environmental Modeling (CREM) (USEPA 2005). In addition to developing modules that facilitate the coupling ("interoperability") of existing macroenviromental models with the various new computational components of MENTOR, in many cases existing macroenviromental models have been adapted/customized for addressing certain novel requirements and applications. For example, the RAMS/HYPACT system was customized (and supplemented with new modules) for applications relevant to emission and transport of contaminants from large fire events (that could alter locally the structure of the atmospheric planetary boundary layer). As a specific example of such an application, an accidental or intentional fire near a hazardous waste site (such as, e.g., nuclear weapons site of the USDOE complex) was considered. Such a fire event could release, in a very short time, substantial amounts of contaminants that have accumulated in the vegetation over a long time period (through various processes of air deposition, root uptake, etc.). In order to address situations of this type, a prognostic meteorological/dispersion model utilizing the RAMS/HYPACT platform was developed and coupled with a forest fire propagation and contaminant emission model (Gurer and Georgopoulos 1998). Figure 4 demonstrates an application of the coupled fire/dispersion model to the conditions of a prescribed fire experiment conducted on December 5, 1975 at the vicinity of USDOE's Savannah River Site (SRS).

Ecological food-web models In addition to developing linkages with environmental fate/transport models, "interoperability modules" were developed for the utilization of information from simulations employing existing food-web models, such as CATS (Traas et al. 1996). Furthermore, customized food-web models were developed to address the needs of special locales or situations (Hunter et al. 2003).

Local multimedia environmental models Special effort has been given, during the MENTOR development effort, on "customizing" environmental modules for the "local" or "subgrid" scale, i.e., to specifically account for phenomena that are relevant to the spatial/temporal scales of human exposure. These modules are mechanistically consistent with the regional models (discussed above) describing the larger scales of environmental fate/transport, over different ambient scales. For example, modules of aerosol physical and chemical processes, that are compatible with those used in regional multiscale photochemical grid models, were developed and incorporated into local-scale plume models. These models have higher resolution and can describe locally important gradients in gas and aerosol concentrations. As a specific application example, sample results from a RPM-AERO (Reactive Plume Model with AEROsol processes model) simulation, which incorporates state-of-the art MENTOR modules for nucleation, condensation, dry deposition, gas/particle partitioning

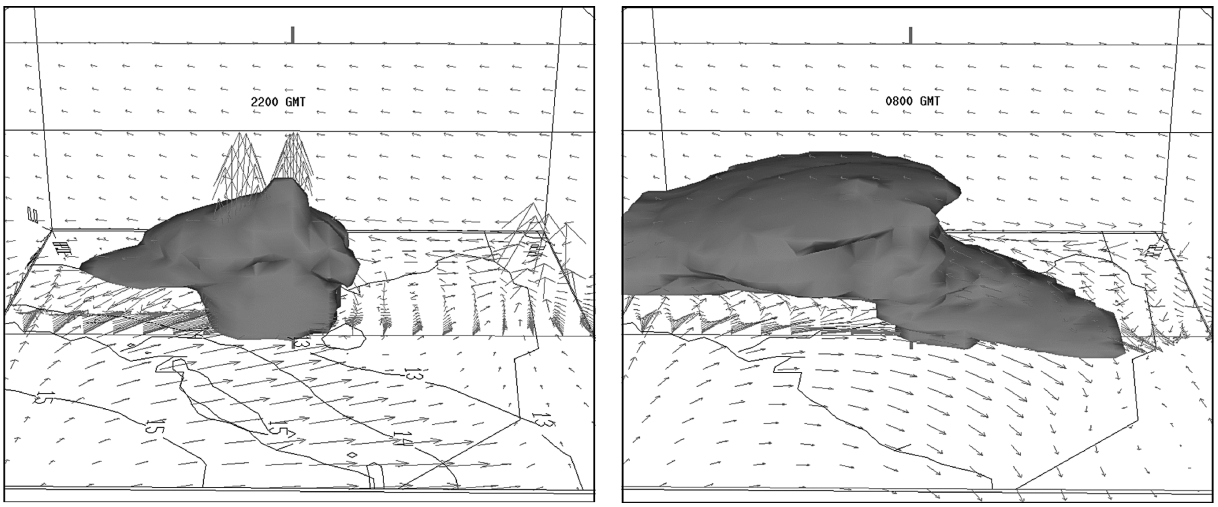

FIGURE 4. 3-D Views of the smoke plume simulation (superimposed to the atmospheric boundary layer wind field) performed with an adaptation of RAMS/HYPACT for a controlled fire that took place in the vicinity of USDOE's Savannah River Site (from Gurer and Georgopoulos 1998).

of organic matter, new particle formation, and secondary organic matter formation, are shown in Figure 5. The figures illustrate the growth in mass, and the change in nucleation rate within a plume. These estimates are applicable to a much finer spatial scale than grid-based models, and they can be used subsequently to improve characterization of individual or population exposures at local scales (Drossinos et al. 2001; Kevrekidis et al. 1999; Lazaridis et al. 2001b, 2005).

Microenvironmental models A series of modules describing the dynamics of microenvironmental processes in a way consistent with the methods and assumptions employed in environmental ("outdoor") fate/transport models, were developed and incorporated in MENTOR. For example, in the past, indoor microenvironmental models have not used the explicit chemical composition of contaminated ambient air, as characterized by photochemical air quality models or ambient monitors,

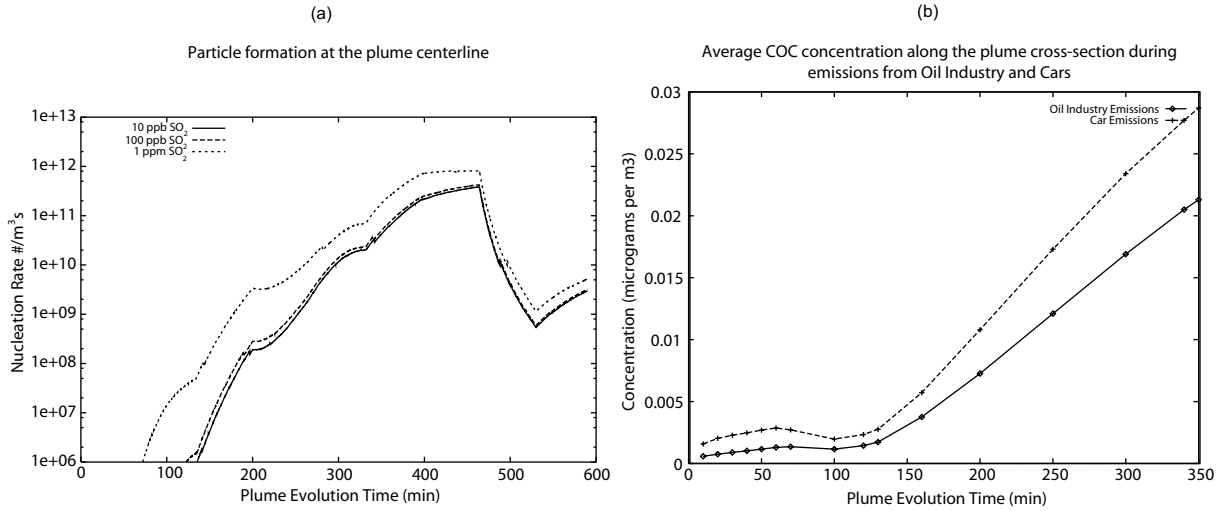

FIGURE 5. Sample calculations of aerosol-in-plume properties performed with the RPM-AERO model: (a) Nucleation rate (particles/m^3s) versus transport time (min) of plume for different initial SO_2 concentrations corresponding to low (10 ppb), moderate (100 ppb) and high (1 ppm) sources; (b) Comparison of the COC production potential due to emissions from vehicle and from oil industry emissions (from Lazaridis et al. 2001b, used by permission).

to examine indoor chemical processes for secondary gas or particle formation and thus simulate total indoor exposure to air pollutants. So, there has been a long-standing need for models of indoor gaseous and aerosol physics and chemistry that are mechanistically consistent with outdoor air quality models. In fact, there are important indoor chemical processes (such as the formation of ultrafine aerosol from the interaction of ozone entrained from outdoors with volatile organics emitted indoors, such as terpenes from household chemicals), which are not accounted for in existing indoor air quality models. So, indoor physics/chemistry models were developed for use within MENTOR that achieve compatibility with outdoor air quality models, and also account for physical and chemical processes that are predominant in the indoor environment. In the end, the goal is to use these models to reduce uncertainty in exposure/dose simulations and define the contributions made from indoor/outdoor air.

As an application example, Figure 6 shows the estimated formation of ultrafine PM indoors due to complex reactions between ozone entrained indoors and VOCs emitted indoors (including α-pinene). This provides a basis for considering the significance of "fresh" aerosol exposure and dose at times and locales that can augment outdoor contributions (Georgopoulos et al. 2002). Ongoing work is testing the performance of the ozone-VOC indoor reaction mechanisms with data collected in a controlled study of human exposure to products of the O_3-VOC reactions (Fan et al. 2003).

Activity pattern/exposure event models To perform applications of MENTOR, and characterize source-to-dose relationships for an actual or virtual "individual" the analyses must be capable of tracking this individual consistently through his/her activities in space and time. Existing person-oriented models typically focus on intake rather than uptake, and, except through empirical methods, do not calculate eliminated dose. Thus, there has been a need, as discussed by Georgopoulos and Lioy (1994), to couple human activities, microenvironmental, and biological processes, in a mechanistically consistent manner to estimate the dose received by a person. MENTOR tools in fact automate many of the estimation steps involved, including dynamic/interactive linkage with activity databases such as CHAD, for a PBEM application. For each simulated individual, the activity diary (if not available from a case-specific study) is selected from CHAD based on the matching demographic attributes (age, gender, employment status, etc.). The METS (Metabolic Equivalent of Tasks) values are then assigned for each activity event to calculate intake needs (such as inhalation rates, water and food consumption). The PBEM framework utilizes an extensive but consistent set of variables and information for source characterization, exposure factors, and human activity patterns

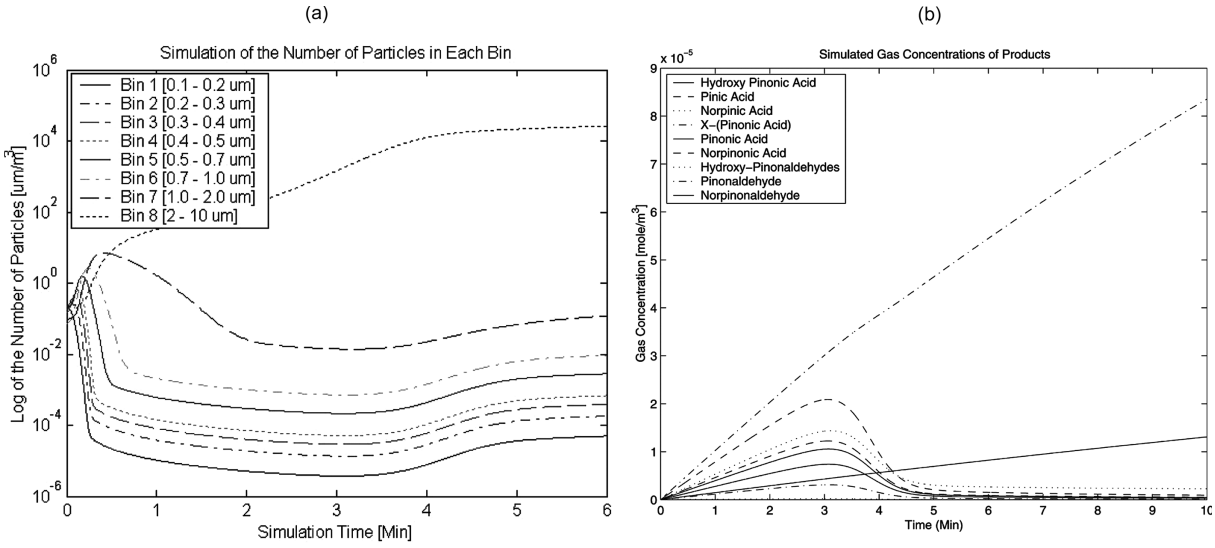

FIGURE 6. Simulation of (a) the growth of different components of the aerosol size distribution and of (b) gas phase concentration of α-pinene, from household cleaning products, resulting from reacting with ozone entrained indoors (from Georgopoulos et al. 2002).

to conduct population exposure assessment of multi-pollutants. This is a primary distinction from previous studies of population exposure assessment, where different exposure factors and activity patterns would be used for different pollutants due to the structure of the software algorithms and codes used in these studies.

Biologically based dosimetry and toxicokinetic models To improve our understanding of contaminant intake, biologically-based dosimetry models must account explicitly for age, gender, as well as physiology and activity variation, as these factors critically influence both the uptake and the disposition/metabolism of xenobiotics. Such explicit consideration, on a "per-individual basis" helps in identifying those subpopulations that may be at higher risk. To accomplish this, MENTOR provides a hierarchy of alternative models, so that the appropriate level of detail, e.g., simple and fast screening models or detailed models that require case-specific information, can be applied to a problem at hand.

Biological models that were developed for use in MENTOR include new modules for gas and aerosol inhalation dosimetry that, for example, consider hygroscopic and chemically reactive aerosols, taking into account transformations that are compatible with the modeling of ambient and indoor air. This allows building of a flexible inhalation framework which has explicit age and gender dependence, for physiologically based pharmacokinetics of volatile and non-volatile contaminants and for aerosol inhalation dosimetry. Considering the age-related issues for PM exposure and health outcomes, these MENTOR modules can be used to improve our understanding regarding differential exposures/doses, and ultimately risks, for special subgroups of the general population. As an example, Figure 7a shows sample calculations from a detailed ("IBEM-oriented") inhalation dosimetry model that considers evolving hygroscopic particles of different sizes, while Figure 7b shows predicted PM2.5 doses from a "PBEM-oriented" module also developed as part of MENTOR (Broday and Georgopoulos 2001, Lazaridis et al. 2001a).

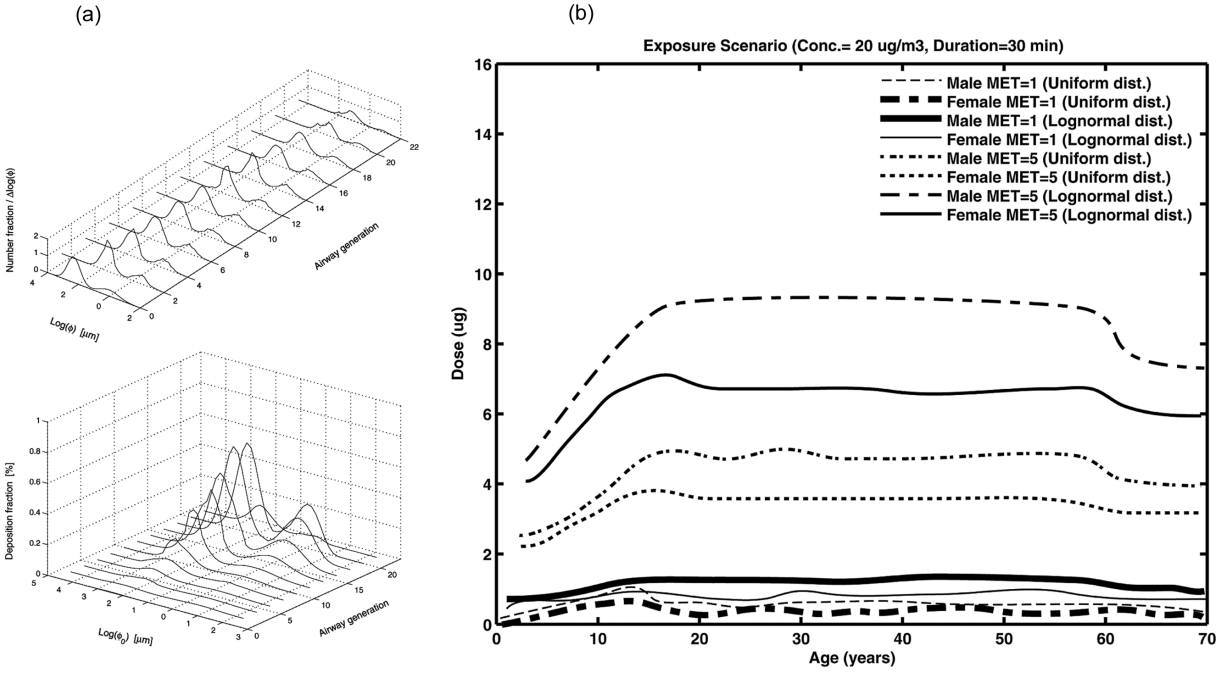

FIGURE 7. (a) Example of respiratory dosimetry module calculation in MENTOR: evolution of PM size distribution in the human respiratory tract via 1D macromodeling. Fine hygroscopic PM concentration/size variation along the conducting airways of the human respiratory tract (persistent vs. deposition) (from Broday and Georgopoulos 2001, used by permission) (b) Dependence of inhaled PM2.5 dose on gender, age, and activity (quantified by MET = Metabolic Equivalent of Tasks) estimated by a new simplified population-oriented module of MENTOR. Calculations show the critical dependence of PM2.5 dose on factors such as the activity level of the individual and the size distribution of the fine particles (from Georgopoulos et al. 2004b).

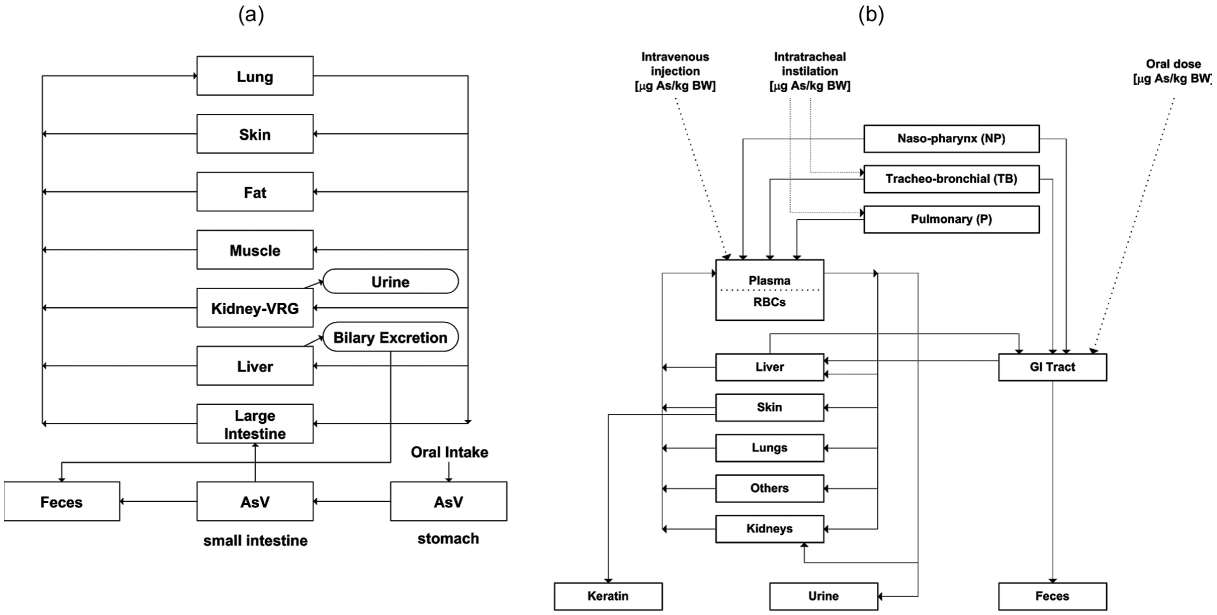

FIGURE 8. MENTOR's modular framework allows alternative biological descriptions: for example, alternative available human PBTK models for arsenic include (a) flow-limited, and (b) diffusion-limited formulations (from Georgopoulos et al. 2005c).

In addition to providing modules with alternative descriptions of respiratory uptake processes, both flow-limited and diffusion-limited PBTK modules for systemic contaminants have been implemented in MENTOR (see, e.g., Figure 8). The availability of modules with such alternative formulations – that are appropriate for contaminants with different physicochemical attributes and exposures of widely different types – allows the exposure/risk assessor to develop simulations customized to the specific case study at hand.

Dose-response models Dose-response modules currently available within MENTOR utilize either empirical information from traditional toxicological studies or attempt to merge, in a quasi-quantitative manner, available mechanistic characterizations of toxicity pathways or modes of action with laboratory data (McGrath et al. 1996). Ongoing efforts focus on the incorporation of molecular level methods and bionomic approaches (see discussion in "The Path Forward" section).

MENTOR Modules – Data Modules

Databases of environmental/microenvironmental quality and attributes, combined with activity, demographics, etc. information are essential in MENTOR applications. Table 2 provides summary information on a sample of the databases currently utilized by applications of MENTOR.

MENTOR Modules – Diagnostic Analysis Tools

Multiscale domain data import/export Environmental Information Systems (EIS, Gunther 1998) are appropriate for traditional environmental impact analyses; however, exposure assessments require, in addition to environmental information, many levels of "receptor (i.e. human) oriented" information (demographics, housing, activity diaries, food and water consumption data, etc.) Structures that merge the Environmental Information System concept with information on exposure routes/pathways and receptor attributes were developed to provide prototypes for the next generation of information support systems for exposure analysis (Exposure Information Systems or EXIS). Prototype EXIS were utilized within MENTOR for applications involving exposures to arsenic, copper, and trichloroethylene. More specifically, these systems link exposure-related calculation modules with (1) databases for contaminant occurrence in a variety of media (drinking water, food, air, etc.), (2) demographic and human activities databases, and (3) geodatabase "engines" that

allow managing/assessing spatial information associated with the preceding data. The development of the EXIS approach followed a recommendation and addressed a major need identified in Georgopoulos and Lioy (1994).

Furthermore, human exposure is associated with conditions within microenvironments that may include contaminants generated by sources or reactions that occur at multiple scales, from regional to local to neighborhood to indoor. As discussed in Georgopoulos and Lioy (1994), to examine human exposure, environmental information is needed at the local level for multiple (long or short) time periods. This requires linking information and models for local and microenvironmental quality with the corresponding macroenvironmental (regional, urban) information and models, in a computationally efficient manner. For example, in the case of regional air quality models, the inputs and outputs are currently becoming available for annual simulations (Graham and McCurdy 2004; Georgopoulos et al. 2005), but are only available at coarse grid resolutions, so there exists a need to simulate smaller space/time domains at higher resolutions for the exposure analysis. The coupling of prognostic and diagnostic atmospheric modeling within MENTOR has allowed the computationally efficient development of meteorological inputs for mid- and long-term application (seasonal/annual) of multiscale photochemical ambient air quality models. The effectiveness and usefulness of coupling prognostic and diagnostic meteorological models for producing high resolution wind fields in an efficient manner was demonstrated in practice by coupling "coarse outputs" from the prognostic model MM5 (a component of the Models-3 system) with the diagnostic wind model CALMET to generate fine resolution meteorological inputs for exposure oriented air quality modeling. Results show that fine resolution (4 km) wind fields produced by the diagnostic model using 36 km prognostic fields as inputs are of comparable accuracy to 4 km resolution prognostic fields (Chandrasekar et al. 2003). Such analyses are used in on-going studies to complete PBEM estimates for seasonal and annual applications.

Integrated efficient sensitivity/uncertainty analysis Quantitative characterization of uncertainties is critical in the source-to-dose modeling process, and traditional Monte Carlo methods (including Latin Hypercube Sampling) may not be feasible or practical when the models employed are complex (e.g. multidimensional dynamic numerical models) or the number of cases (e.g. for simulations involving large numbers of virtual individuals) that need to be computed is very large. Thus, there is a critical need for computationally efficient methods for performing distributional/uncertainty analysis. In response to this need, the Stochastic Response Surface Method (SRSM) was developed for efficient analysis of uncertainty propagation (Isukapalli et al. 1998). Furthermore, when the models used are coded in either Fortran or C, further efficiencies can be obtained by applying SRSM in combination with sensitivity analysis software (ADIFOR/ADIC) employing automated differentiation of computer code, developed at Argonne National Laboratory (Bischof et al. 1994). The SRSM method was utilized in various applications, including atmospheric chemistry and transport models, physiologically based toxicokinetic models, ground water flow and contaminant transport models, etc. The results indicate that the SRSM approach shows close agreement with "traditional" Monte Carlo uncertainty analysis results, while requiring a significantly lower number of model runs (Balakrishnan et al. 2002, 2003, 2005).

Variability characterization For exposure assessment purposes, ambient pollutant concentration information available at a local level (such as census tract or neighborhood) needs to be used as input to microenvironmental models for the estimation of population or individual exposures. However, typical field monitoring data, and associated regional environmental quality model estimates, provide spatial characterizations of concentration fields at "grid" levels that are too coarse for exposure characterization; so there is a need to further characterize local "subgrid" variability, with "subgrid" referring to resolutions in space that are higher than those typically provided by numerical models and/or monitor networks. To provide such resolution, Spatio-Temporal Random Field (STRF) methods were incorporated in MENTOR for characterizing local (subgrid) variability of ambient properties (including contaminant concentrations). These modules were designed and tested for the optimal interpolation of values modeled on a regular grid or monitored at irregular observation locations and also for incorporating local ("subgrid") effects from observations in the modeled estimates by "fusing" modeling with available "hard" (measurements) and "soft" (ranges)

information. The STRF approach (Christakos and Vyas 1998a, 1998b; Vyas and Christakos 1997) interpolates information and/or data in space and time simultaneously. This method can adjust for information on "temporal trends", which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Furthermore, the STRF method can optimize the use of data that are not uniformly arranged in either space or time. STRF was extended into the Bayesian Maximum Entropy (BME) framework (Serre 1999; Serre and Christakos 1999; Christakos and Serre 2000) that has also been incorporated in MENTOR.

As an example, STRF and BME-based methods were employed to optimally interpolate combined spatial and temporal information from both environmental quality model outputs and from data obtained by monitoring networks. Figure 9 shows fine scale (<3 km) interpolation of groundwater monitor data preferred to develop hydraulic conductivity parameters that are needed to run groundwater models at a local scale (Georgopoulos et al. 2004b, 2005; Vyas et al. 2004).

Bayesian model/data assimilation Georgopoulos and Lioy (1994) highlighted the need to invest in the development of tools for rapid optimization of modeling results. It is well known that uncertainty in model parameters can be reduced by optimal parameter estimation or "calibration" using laboratory and field data. For models with few parameters this can be done by traditional statistical methods (such as maximum likelihood.) However, for complex models that involve multiple correlated parameters, more flexible techniques are needed. Bayesian Markov Chain Monte Carlo (BMCMC) techniques offer a very promising alternative for optimal parameter estimation (as well as "input reconstruction" in "inverse problems"), and a set of BMCMC simulation support modules was developed for MENTOR. Furthermore, since MCMC techniques can be very computationally demanding when the models employed are complex, as they require several thousands of model runs, a new approach was developed that couples MCMC with SRSM to achieve faster convergence

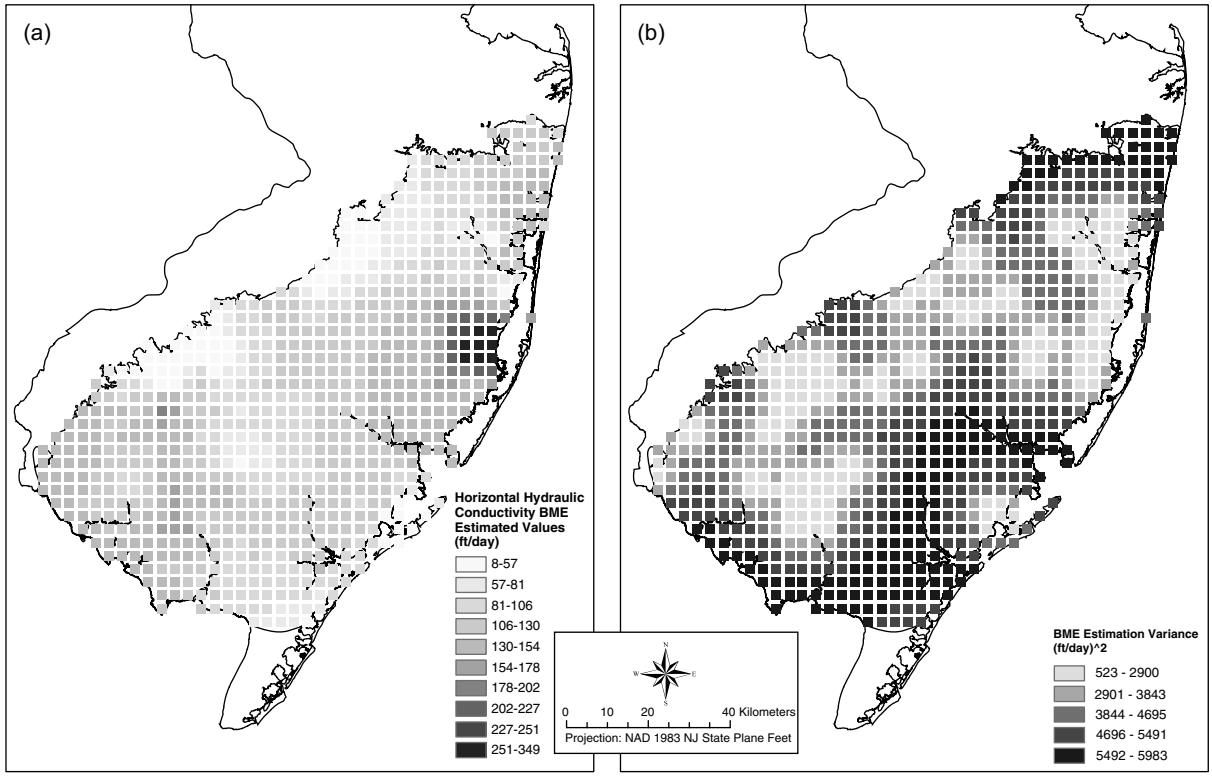

FIGURE 9. Map of local scale estimates of horizontal hydraulic conductivity (a) means and (b) variances, for the Kirkwood-Cohansey aquifer in New Jersey, using data provided by NJDEP and obtained from USGS Regional Aquifer-System Analysis (RASA) Reports: the local scale interpolation employed Bayesian Maximum Entropy (BME) techniques within MENTOR (from Vyas et al. 2004, used by permission).

of MCMC estimates. The BMCMC tools of MENTOR were applied to PBTK modeling of benzene, and to finite element groundwater transport and fate modeling, in combination with SRSM (Balakrishnan et al. 2003).

Treatment of missing data The problem of rational and systematic handling of "missing" data (including those resulting from monitor/sensor failures, from levels below detection limits, etc.) is very important in almost every environmental application field. As a specific new example of this type of problem, DNA microarray technology led to an explosion of gene expression data (including – and forthcoming – data representing responses to environmental stressors). However, virtually every experiment contains missing entries arising from blemishes on the microarray, and values of missing entries must be estimated before analytical methods such as clustering can be applied.

In response to this problem an improved missing value estimation method was developed; it is based on Gaussian mixture modeling, and was shown empirically to be more accurate than existing methods. A computational implementation of this method was incorporated as a stand-alone module of MENTOR (Ouyang et al. 2004).

Systematic model reduction A special focus of the MENTOR project has been on the development and implementation of algorithms for sensitivity analysis that can provide information for the systematic simplification of complex models and "construction" of Fast Equivalent Operational Models (FEOMs). Traditionally, two classes of approaches are applied to perform sensitivity/uncertainty analysis: perturbative sensitivity analysis and Monte Carlo sampling (Saltelli et al. 2000). In both cases the model input variables are characterized by distribution functions and the goal is to calculate the mean and variance of the target model output. Within MENTOR, SRSM provides an efficient way for implementing these approaches. Furthermore, the High Dimensional Model Representation (HDMR) method, developed by Rabitz and coworkers (Rabitz and Alis 1999; Li et al. 2001; Wang et al. 2003), provides a new family of tools (also coded in the MENTOR toolbox), available for sensitivity analysis and subsequent development of simpler, fast, but accurate "substitute" models (FEOMs). The HDMR method provides a "global" understanding of which model variables are significant in a dynamic system, and how they are interrelated within the system. For a complex model with several parameters/inputs, it is important to identify those with the greatest effect on the model outputs. Applications of HDMR within MENTOR include atmospheric chemistry modeling; groundwater flow modeling; PBTK modeling (arsenic); and coupled multimedia microenvironmental and PBTK modeling (TCE). Sample results, shown in Figure 10, depict the successful development of a FEOM for calculation of arsenic, employing using physiologically based toxicokinetics, for use in population exposure assessments. The FEOM calculation is about 80 times faster than the original arsenic PBTK model, while producing very similar dose distributions of model outputs (Li et al. 2001, 2003a, 2003b; Wang et al. 2003, 2005; Georgopoulos et al. 2005c).

Diagnostic database and model analysis and evaluation Databases that resulted from comprehensive ("multidimensional") exposure studies, such as NHEXAS, include a number of highly correlated variables. Further, they include a large number of both continuous and categorical variables, whose observations are often below the detection limits. Comprehensive exposure models, such as the available computational implementations of MENTOR (e.g. MENTOR/SHEDS-1A and MENTOR/SHEDS-4M) produce outputs of similar complexity as the above studies, but much larger in database size. Clearly, traditional statistical techniques are often not sufficient for analyzing these databases, and thus there is a need to develop and/or apply novel analysis techniques. Existing methods such as Classification And Regression Tree (CART), and new methods developed by the MENTOR group, based on HDMR, were incorporated in the MENTOR toolbox for application to complex exposure databases.

Figure 11a and b show application of CART and HDMR methods to the analysis of NHEXAS Region-V data: they were used to identify patterns relating arsenic levels in exposure media (food, water, air, dust) and in biomarkers (urine) and to corroborate the analysis of predictive MENTOR-based modeling (Roy et al. 2003; Georgopoulos et al. 2005c).

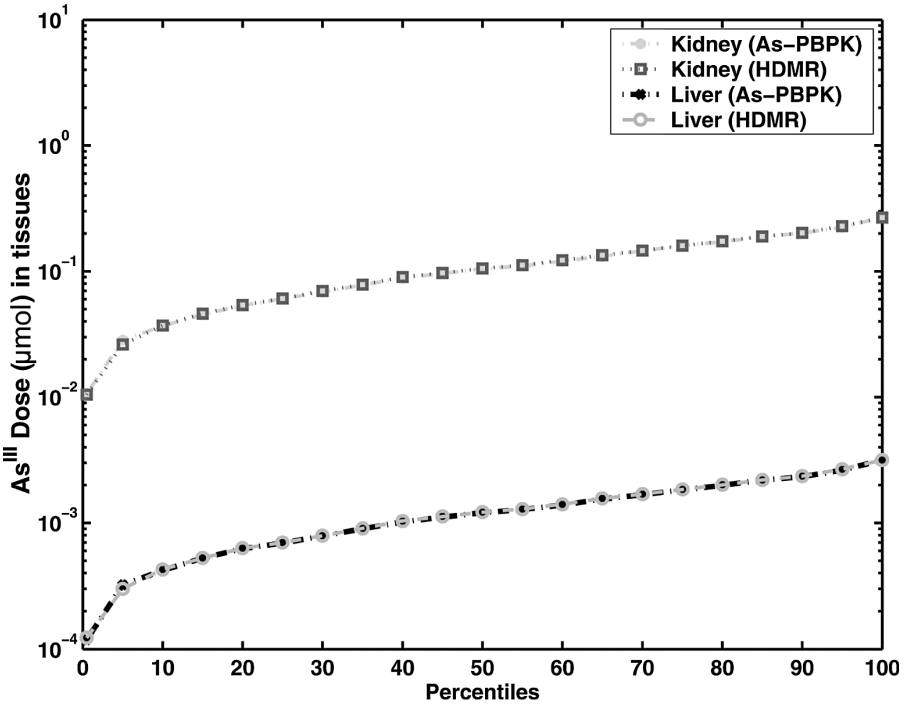

FIGURE 10. Application of a Fast Equivalent Operational Model (FEOM) developed via High Dimensional Model Representation (HDMR): comparison of trivalent arsenic (AsIII) dose distributions calculated by a "full" As-PBTK model and an HDMR reduced model for a population of 1000 people (from Georgopoulos et al. 2005c). The predicted distributions of target tissue (liver and kidney) doses from the two approaches are practically indistinguishable.

Applications of MENTOR

Mechanistic source-to-dose analysis of exposure assessment for co-occurring fine airborne PM, ozone, and air toxics There is a critical need to characterize cumulative/aggregate exposures and doses of co-occurring air pollutants such as ozone, PM, and air toxics; however this must be done in a mechanistically consistent manner in order to quantify (the often nonlinear) source-to-dose relationships. MENTOR has been used to couple together existing USEPA models and methods while at the same time filling gaps in the source-to-dose sequence (an "added value" approach to source-to-dose modeling).

In the Philadelphia case study (Georgopoulos et al. 2005a, 2005b) the following models were employed within MENTOR: the MM5 mesocale prognostic meteorological model (a component of USEPA's Models-3); the Sparse Matrix Operator Kernel Emissions (SMOKE) emission inventory processing system (a component of Models-3); the Models-3/CMAQ multiscale photochemical air quality model; MENTOR's tools for optimal spatiotemporal interpolation of ambient PM and ozone concentration estimates from Models-3/CMAQ at the census tract level; USEPA's SHEDS modeling methodology, recoded/adapted in the MENTOR framework and interactively linked with USEPA's CHAD; and MENTOR's novel age, gender, and activity dependent inhalation dosimetry modeling components for population exposures. Demonstrations were completed for the city of Philadelphia, PA by Georgopoulos et al. (2005a; 2005b), for a two-week period during the summer of 1999 and for the full year of 2001. Example simulation results presented in Figure 12a and b show that indoor sources dominate contribution to the total doses of PM2.5, while the time spent outdoors dominates contributions to total doses of O_3 at higher percentiles.

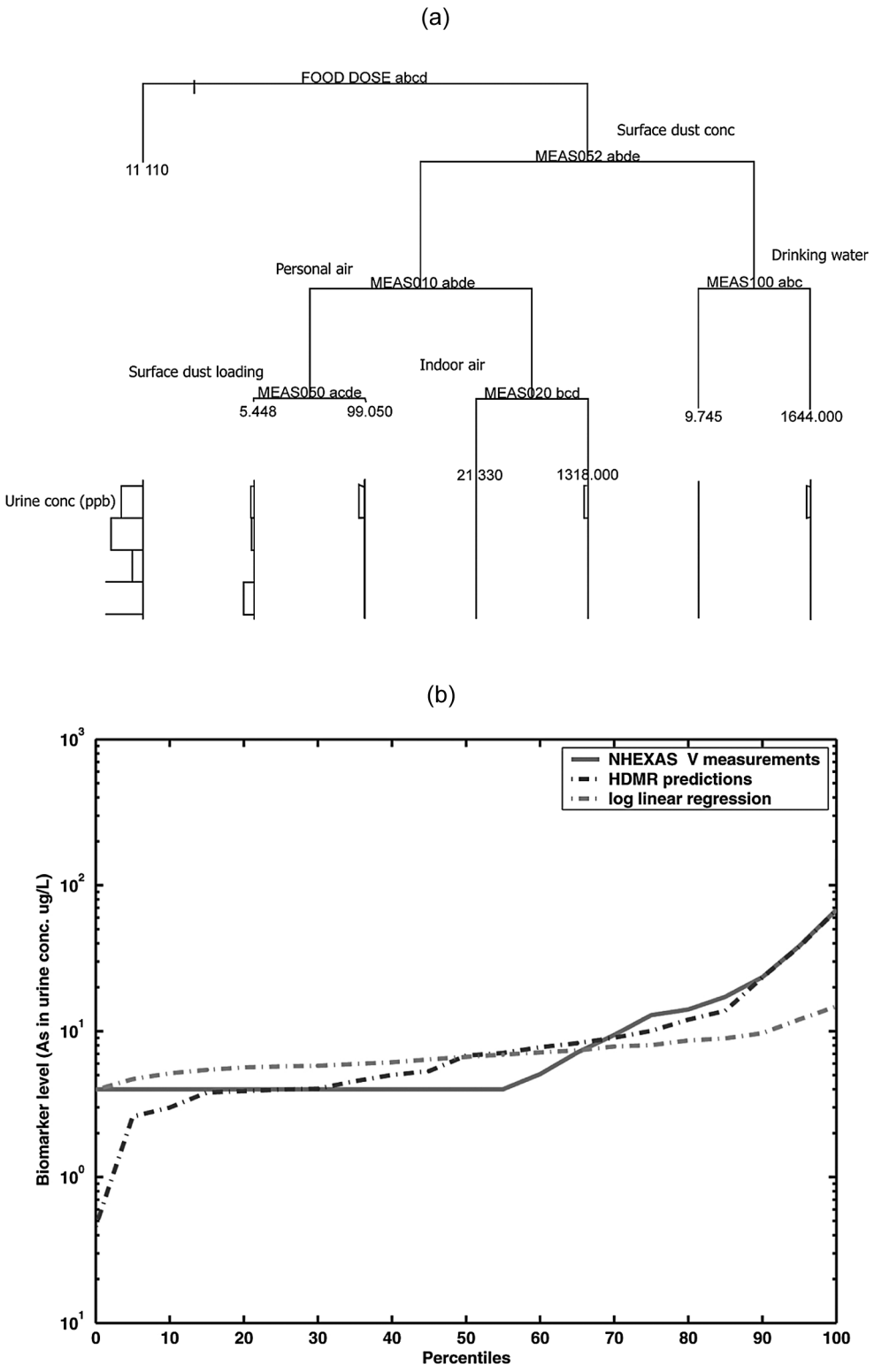

FIGURE 11. (a) An example of using Classification and Regression Tree (CART) to identify patterns in the NHEXAS Region-V data for arsenic in exposure media (food, water, air, dust) and biomarkers (urine), to corroborate the analysis of predictive MENTOR modeling (Georgopoulos et al. 2005c); (b) Comparison of cumulative distributions of total arsenic in urine concentrations (μg/L) calculated with the High Dimensional Model Representation (HDMR) method and with log linear regression, both using the measured multimedia (air, soil, dust, food, and beverage) exposure data as the predictors, versus the corresponding NHEXAS Region-V measurements (unpublished results).

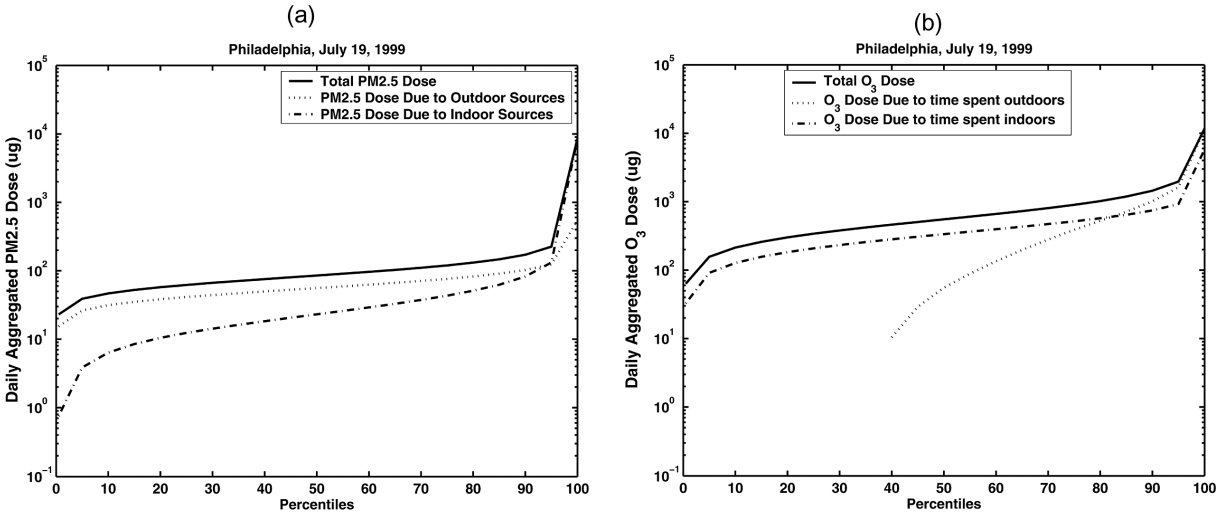

FIGURE 12. Cumulative distribution functions of (a) PM2.5 total doses, doses from outdoor sources, and doses from indoor sources; (b) O_3 total doses, doses due to time spent outdoors, and doses due to time spent indoors. The distributions were developed by applying MENTOR to 482 census tracts in the urban Philadelphia area; results are shown for July 19, 1999. 500 "virtual individuals" were simulated for each of the 482 census tracts used in the study. Models-3/CMAQ predictions interpolated to census tracts via MENTOR's Spatio-Temporal Random Field (STRF) modules were used as outdoor concentrations. The doses were calculated using MENTOR's age, gender, and activity dependent respiratory dosimetry modules (from Georgopoulos et al. 2005a, used by permission).

Evaluation of alternative regional ozone (and PM) control strategies and alternative formulations of air quality standards via population exposure metrics Human exposure is "the one and only element that can link "risk assessment" to "risk management" to "accountability" when the objective is to protect human populations (not only the general population, but also the susceptible populations and the highly exposed populations) from environmental contaminants" (Foley et al. 2003). Therefore, there is a need to evaluate emission control strategies from the perspective of population exposures. Tools associated with MENTOR have been coupled with Models 3/CMAQ to calculate various potential outdoor exposure estimates for populations, appropriate for evaluating emission control strategies. This allows assessing the effect of a proposed emission control strategy not only on ambient air pollution levels but also on related population exposures. Simulations performed using Models 3/CMAQ in MENTOR, focusing on the Eastern United States for the summer of 1999 (Figure 13), show that emission control strategies aiming to meet the 8-hr ozone standard (NOx intensive) are also effective in reducing potential population exposures to ozone (Foley et al. 2003; Purushothaman and Georgopoulos 1999a, 1999b).

Assessment of multisource/multipathway exposures of individuals and populations to inorganic and organic arsenic To understand and quantify the contribution of different sources to the multipathway exposures and doses involving multimedia contaminants one must complete complex analyses that, by necessity, address the presence of contaminants simultaneously in food, water, air, soil, etc. A prototype source-to-dose application of MENTOR was developed and applied to understand the significance of different pathways on arsenic exposures. The analyses combined and extended the SHEDS approach in a multimedia framework that is part of MENTOR and dynamically link the modules that calculate exposure-related metrics with physiologically based calculations of the toxicokinetics of different forms of arsenic. This system incorporates comprehensive relational databases and geodatabases of environmental, microenvironmental, demographic, and human activities indicators.

Prototype source-to-dose assessment case studies were performed for populations in New Jersey, Arizona and Ohio. A unique aspect of the MENTOR/SHEDS-4M study of arsenic exposures was that it took a major step beyond any previous similar analysis, by calculating target tissue dose (and corresponding biomarker levels) with PBTK modeling for the entire population considered.

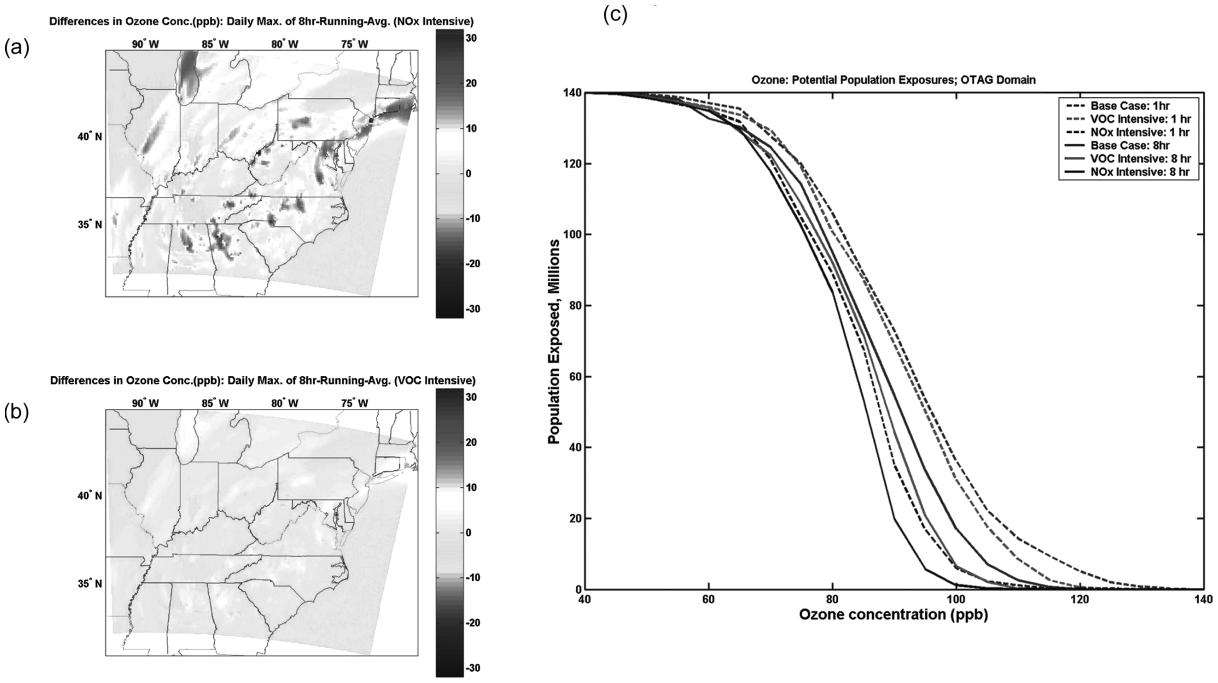

FIGURE 13. Relative effectiveness of "across-the-board" (a) "NOx-intensive" versus (b) "VOC-intensive" source emission controls in reducing daily maxima of 8-hour average ambient ozone concentrations, and (c) comparison of both controls in reducing potential outdoor ozone population exposures. ("NOx-intensive" controls refer to a hypothetical 75% reduction of all NOx emissions and 25% reduction of all VOC emissions in the modeling domain; "VOC-intensive" controls refer to 75% reductions in VOC and 25% in NOx emissions). "NOx-intensive" controls were found to be more effective in both reducing maxima of ambient concentrations and for reducing potential population exposures at levels above the 1 and 8-hour ozone standards (from Foley et al. 2003, used by permission).

Such applications of MENTOR/SHEDS-4M offer the advantage of allowing model evaluation against biomarker field measurements. Indeed, the exposure-to-dose modeling components of MENTOR were evaluated by comparing distributions of the total arsenic amounts in urine estimated for the residents of Franklin County, Ohio with those derived from biomarker measurements collected through the NHEXAS Region-V study for that County. As shown in Figure 14a the distributions of biomarker levels calculated from MENTOR and from the NHEXAS measurements are within a factor of 5 or less. Given the uncertainty involved in the source-to-dose estimation procedure, this agreement should be considered satisfactory. Furthermore, Figure 14b shows the contribution of individual pathways to exposure (intake): food intake and drinking water consumption routes appear to be the major pathways for the total arsenic exposure (with food dominating even for inorganic arsenic), while the nondietary and inhalation routes act as minor contributors to the total exposure (Georgopoulos et al. 2005c).

Microenvironmental characterization and control of potential secondary emissions and impact of Chemical Warfare Agents There is a need for developing appropriate emergency response plans for receiving victims from emergency events including toxic chemicals (such as chemical weapons agents) and simultaneously protecting healthcare professionals. Such plans should include protocols and standards for personal protective equipment (PPE) for healthcare workers.

As an example, MENTOR provides tools that can be used for probabilistic assessment of potential exposures in the case of a release of a toxic chemical or a Chemical Warfare Agent (CWA). Thus, comprehensive scenarios can be modeled with likely distribution estimates for the "secondary" release of contaminants from the victims and provide estimates of possible exposures to emergency responders and healthcare workers. As a specific case study, Figure 15a shows a plausible distribution of mass deposition on victims from the hypothetical release of sarin, and Figure 15b shows the corresponding calculated integrated total exposure of healthcare workers to sarin as

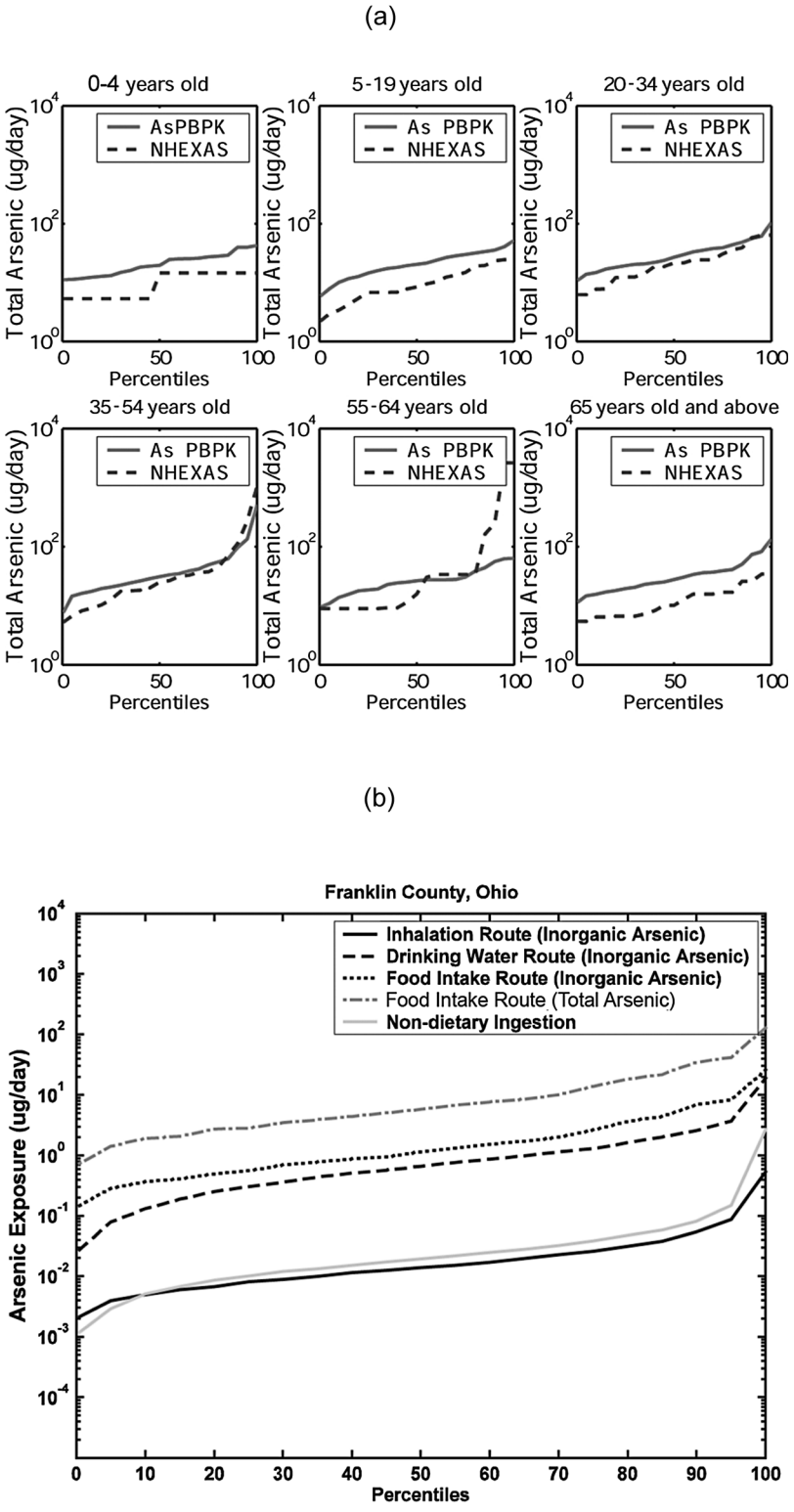

FIGURE 14. (a) Comparison of cumulative distributions of total arsenic amount in urine predicted from MENTOR/SHEDS calculations and observed in NHEXAS measurements for six age groups in Franklin County, OH. (b) Cumulative arsenic (total and inorganic) exposure distributions from inhalation, food intake, drinking water consumption, and non-dietary routes for Franklin County, Ohio (calculated with the MENTOR/SHEDS population based model) (from Georgopoulos et al. 2005c).

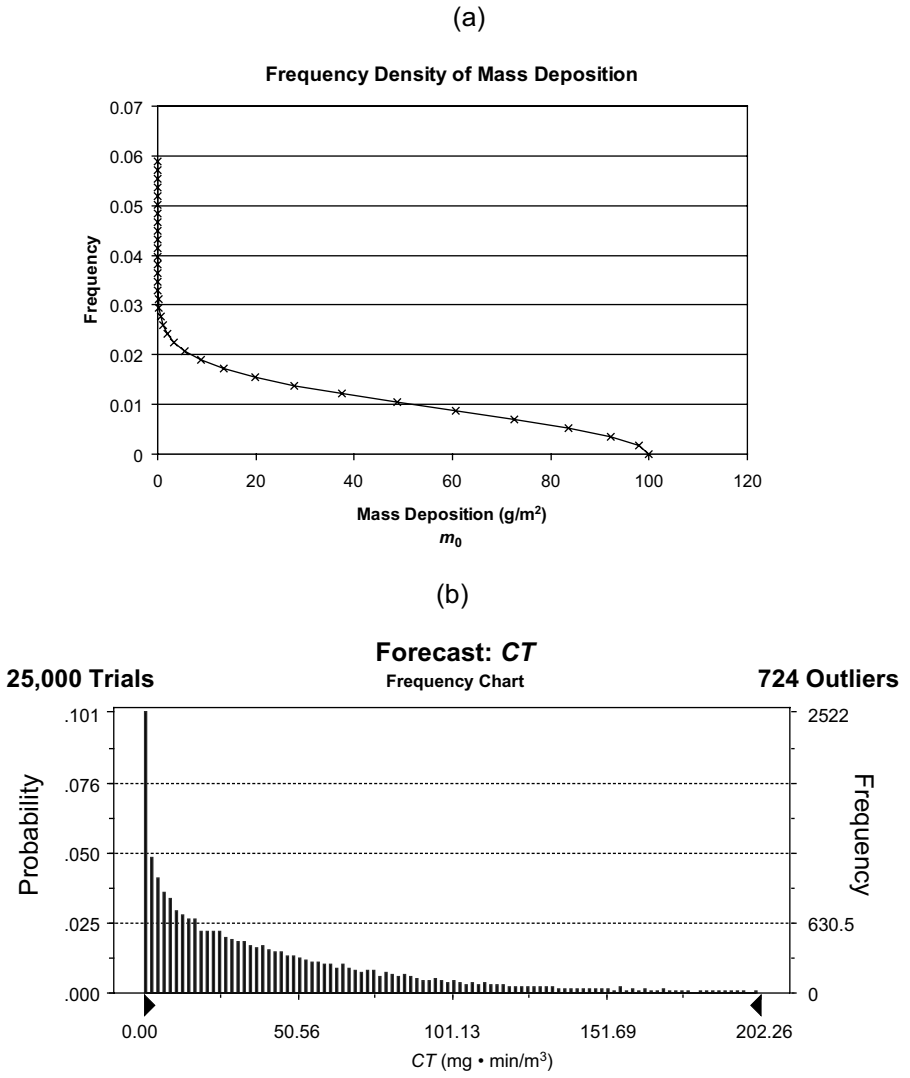

FIGURE 15. (a) Frequency density of initial mass deposition (m_0) of sarin on to victims of a hypothetical situation involving the release of a Chemical Warfare Agent (CWA). This distribution describes the frequency with which victims will be contaminated with a specific amount of sarin, assuming a uniform "density" of people where the likely mass deposition of the CWA decreases as the radial distance increases from the dissemination device. (b) Monte Carlo forecast of total integrated exposure concentration (*CT*) of sarin when a triangular distribution represents the mass deposition (m_0). The time-integrated exposure concentration is the sum of exposure concentration as contaminated patients file past medical personnel. The contaminated body surface area is assumed to be 20%, which represents a potential exposure to healthcare workers when victims immediately disrobe (from Georgopoulos et al. 2004, used by permission).

contaminated patients file past them following the incident. These simulations were used to develop guidelines for decontaminating patients exposed to a CWA prior to entering an emergency room facility, including identification of optimal Personal Protection Equipment (PPE) level for the emergency response personnel, for different stages of the decontamination process (Fedele et al. 2003; Georgopoulos et al. 2004).

Reconstruction of the plume from the World Trade Center fire and collapse following the terrorist attack of 9/11/2001 (a collaborative effort of EOHSI and USEPA-NERL) In the aftermath of the attack on the World Trade Center, it became apparent that there was a need to understand the extent and patterns of exposures associated with the release of gaseous and particulate contaminants from the collapse and the fires that followed for use in epidemiological investigations and risk

assessments. A plume reconstruction using the RAMS/HYPACT system was performed as a first step in the effort to support future studies requiring exposure estimates for various segments of the population. Figure 16 shows the instantaneous "snapshots" of the simulated plume at 13:00 EDT on 9/11, 12, & 13. Currently, the results are being tailored to construct exposure profiles for individuals that may have come in contact with the plume from during the first days to one month after the attack. (Lioy et al. 2002; Lioy and Georgopoulos 2003; Georgopoulos 2003; Offenberg et al. 2004; Wolff et al. 2005).

The Path Forward

In order to enhance "bi-directional" source-to-dose analyses of exposure and biologically effective dose, state-of-the-art Computational Toxicology methods (ebCTC 2005) are now being coupled with MENTOR, as depicted schematically in Figure 1. Such methods are expected to provide new computational tools and quantitative metrics on the potential of chemicals to affect biochemical pathways of concern in the sequence from source-to-dose-to-effect and vice-versa. Included are biologically based toxicokinetic modules and the linkages with quantitative characterization of the toxicodynamic processes for contaminants (USEPA 2003). Computational toxicology methods are expected to provide better characterizations of chemical transformation and metabolism, better diagnostic/prognostic molecular markers, improved dose metrics, characterization of toxicity pathways by using genomics, proteomics, metabonomics, etc. data.

The current version of the MENTOR toolbox incorporates various methods and computational tools needed for PD and PBTK modeling for individuals and populations. Included are (1) uncertainty and intra- and inter-individual variability characterization of biological disposition processes; (2) Bayesian model/data fusion methods for PBTK models; (3) analysis of biomarker exposure and effect data; and (4) analysis of gene expression microarray data. Planned expansion of the MENTOR toolbox will eventually couple with state-of-the-art tools of computational chemistry, with focus on Quantitative Structure Activity Relationships (QSARs), and cellular/molecular level systems biology; these topics were not covered in Georgopoulos and Lioy (1994) but are becoming of critical importance with advances in bionomic technologies and data.

Because MENTOR is designed to facilitate the set-up and performance of source-to-dose simulations, various tools were or are being developed specifically to provide compatible/consistent analysis that will couple with modeling frameworks for computational toxicology. The intent is to reduce uncertainties in dose estimations that can be used to better understand the implications of exposure within the source-to-effect continuum (sequence) described by Lioy (1990, 1999).

Gene expression data can be analyzed through a variety of methods that include: quality filtering (eliminating low quality spots or expression data); normalization (allowing cross-experiment comparison); statistical analysis (identifying differentially expressed genes between treated/exposed and control samples); clustering (discovering gene clusters and coexpressed genes); and classification (constructing predictive models based on gene expression profiles and "marker" gene identification). Clustering represents a classical approach of "unsupervised learning" and is based on the hypothesis that genes in a cluster share similar functions to identify functions for uncharacterized genes or coexpressed genes. Classification represents "supervised learning" and is generally based on the construction of an empirical model based on a set of samples with known endpoint and gene expression data; then the endpoint for an unknown sample is predicted based on its gene expression data using the model. Various classification approaches are available, including Soft Independent Modeling of Chemical Analogy (SIMCA); Artificial Neural Network (ANN); K-Nearest Neighbor (KNN); Decision Tree Methods; Support Vector Machines (SVMs); Fisher's Linear Discriminant (FLD); etc. Most methods generate similar results.

Quantitative Structure Activity Relationships (QSARs) are conceptually based on the "similar property" principle which states that chemicals with similar structures are likely to exhibit similar biological activities. The general procedure in applying QSAR involves two steps: characterization of the molecules under investigation using computational, chemical, and biological methods, and application of chemometric approaches to explore data patterns or to establish the relationships between structure and activity (or property). QSAR methodologies generally include a three-level

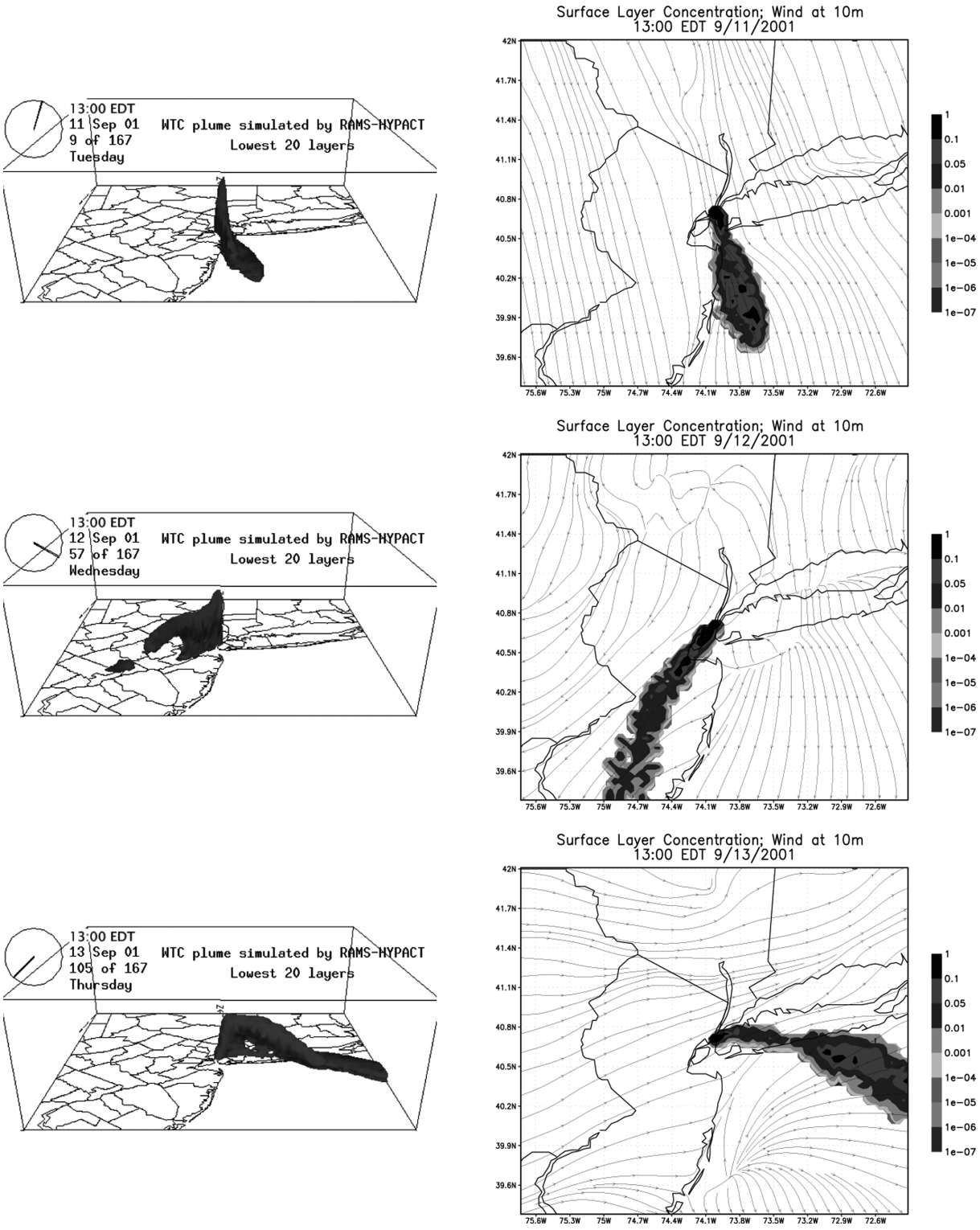

FIGURE 16. Instantaneous views (3-d, left; surface layer normalized concentrations, right) of the World Trade Center plume location and extent, simulated using the RAMS/HYPACT prognostic meteorological and particle dispersion models (from Huber et al. 2004, used by permission).

characterization of (a) chemical structure, (b) physicochemical properties, and (c) biological activity. The ongoing coupling of QSAR techniques with MENTOR will be used to (1) reveal linear and nonlinear structure-activity relationships and handle both small or large, and "noisy", data sets (e.g., Robust Polynomial Neural Network (RPNN) approach); (2) capture ligand-based and receptor-based information, without requiring reformulation as more biological data become available (e.g., Shape Signatures approach); and (3) detect patterns in diverse sources of data including biological (e.g., microarray), chromatographic, and spectral sources (e.g., Pattern Recognition Toolkit).

CONCLUSIONS

Since the 1994 publication of the conceptual framework for source-to-dose modeling of exposures to contaminants, the Computational Chemodynamics Laboratory of EOHSI (http://ccl.rutgers.edu has been able to systematically develop, and demonstrate through case studies, an open computational toolbox (MENTOR) that can assist in analyzing a range of environmental health issues. This toolbox has achieved the basic recommendations set forth by Georgopoulos and Lioy (1994). In addition, it has begun to incorporate new methods for analyzing genomic and other molecular level data to improve dose estimation. MENTOR can be used to build integrated systems, that link the results of studies in various disciplines, to obtain a multifaceted understanding of environmental health problems. In particular MENTOR addresses the need for customized systems, from screening to comprehensive, which can be applied to address multimedia aggregate and cumulative exposure route issues. The examples presented in this manuscript illustrate the wide diversity of problems that have been studied using MENTOR. Finally, MENTOR has demonstrated that incorporation of both existing and new models within a unified probabilistic source-to-dose system can be used to develop and evaluate applications and achieve results faster than through the traditional development of new models.

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